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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/831,954 | 06/25/2001 | Hubert Jan Jozef Loozen | O/98414-US | 9900 |

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| EXAMINER | |
|---|---|
| JIANG, SHAOJIA A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | |

DATE MAILED: 11/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/831,954 | LOOZEN ET AL. | |
| | Examiner | Art Unit | |
| | Shaojia A. Jiang | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,7,8 and 13-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,7,8,13 and 15* is/are rejected.

7)☒ Claim(s) *2,4,14 and 16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This Office Action is in response to Applicant's amendment and response filed on August 23, 2005 wherein claim 8 has been amended.

Claims 5-6 and 9-12 are cancelled previously.

Currently, claims 1-4, 7-8 and 13-16 are pending in this application and under examination on the merits.

Applicant's amendment filed on August 23, 2005 with respect to the rejection of claim 8 made under 35 U.S.C. 112 second paragraph for the use of the indefinite recitation, i.e., "inducing ER-$\alpha$ agonist activity and EP-$\beta$ antagonist in a patient" of record stated in the Office Action dated May 16, 2005 have been fully considered and found persuasive to remove the rejection since the claim has been amended to remove the indefinite recitation. Therefore, said rejection is withdrawn.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 7-8, 13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lobaccaro et al. (of record in the previous Office Action).

Lobaccaro et al. teach the active compounds, 11β-n-alkyl estradiol having ethyl, butyl, or decyl as $R_{11}$, which are homologs of the instant compounds, and their compositions. Lobaccaro also teaches that these compounds having $R_{11}$ ethyl, butyl, or decyl, are known estrogenic compounds and also show antiestrogenic activity, and their compositions. See abstract, Scheme 1 compound 5b on page 2218, Table 1 on page 2219, Table 2 on page 2221, and the 4th paragraph of page 2224. Lobaccaro et al. further teaches that the substituent at the 11β-position increase and improve the binding affinity for the estrogen receptor (ER), and that the length of the11β-n-alky arm affects the binding affinity for the estrogen receptor and these compounds show EP-β antagonist and ER-α agonist activity (see page 2219 the right column to page 2221, Table 2).

Lobaccaro does not expressly disclose the particular 11β-n-alkyl estradiol herein having a length of from 5-9 carbon atoms, and the employment of these estradiol in a method for treating estrogen deficiency disorders and a method of treating estrogen deficiency disorders by inducing ER-α agonist activity and EP-β antagonist activity in a patient in need thereof.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular 11β-n-alkyl estradiol herein method for treating estrogen deficiency disorders and a method of inducing ER-α agonist activity and EP-β antagonist activity in a patient in need thereof.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the particular 11β-n-alkyl estradiol having a length of

from 5-9 carbon atoms in a method for treating estrogen deficiency disorders and a method of inducing ER-α agonist activity and EP-β antagonist activity in a patient in need thereof, since the estradiols of Lobaccaro having 2, 4, and 10 carbons at 11 -β-position are known estrogenic compounds and also show antiestrogenic activity, and thus one ordinary skill in the art would have expected the estradiol compounds of Lobaccaro to be useful in the method for treating estrogen deficiency disorders since estradiol compounds are well known to be useful the method for treating estrogen deficiency disorders.

Moreover, the substituent at the 11 -β-position in the compounds of Lobaccaro is known to increase and improve the binding affinity for the estrogen receptor according to Lobaccaro et al. Estrogen receptor affinity is known to discriminate two estrogen receptors, ER-α and EP-β. Further, the compounds of Lobaccaro et al. show ER agonist activity and ER antagonist activity. Therefore, one ordinary skill in the art would reasonably have expected the estradiol compounds of Lobaccaro to be useful a method of treating estrogen deficiency disorders by inducing ER-α agonist activity and EP-β antagonist activity in a patient.

The structure of the instant compounds having a length of from 5-9 carbon atoms in $R_{11}$, is substantially similar to the structures of their homologs having ethyl, butyl, or decyl as $R_{11}$ in Lobaccaro. Moreover, the substituent at the 11β-position is known to increase and improve the binding affinity for the estrogen receptor, and the length of the 11 -β-n-alky arm affects the binding affinity for the estrogen receptor to have ER agonist activity and ER antagonist ER-α agonist activity. Therefore, one of ordinary skill in the

art would have reasonably expected that the compounds of Lobaccaro modified from having the length of 2, 4, and 10 carbons at 11 to the length of 5-9 carbons at 11 would have possess the same or similar activity as their homologs because of the substantially close structural relationship. It has been settled that the addition of $CH_3$ or several $CH_2$ groups to a known compound is not ordinarily patentable and prima facie obvious. See *In re Wood*, 199 USPQ 137. Further, Lobaccaro has clearly provided the motivation to the structure modification herein since he teaches that the substituent at the 11 -β-position increase and improve the binding affinity for the estrogen receptor, and the length of the11β-n-alky arm affects the binding affinity for the estrogen receptor, and also affects ER agonist activity and ER antagonist activity.

Thus, one of ordinary skill in the art would have reasonably expected that the instant compounds would be useful in the method for treating estrogen deficiency disorders and the method of inducing ER-α agonist activity and EP-β antagonist activity in a patient.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Claims 1, 3, 7-8, 13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Napolitano et al. (of record in the previous Office Action).

Napolitano et al. teaches the active compounds, 11β-substituted estradiol derivatives having $R_{11}$ with less than 5 carbon atoms, which are homologs of the instant compounds, and their compositions. Napolitano et al. teaches that 11β-substituted estradiol derivatives therein are known estrogenic compounds as the estrogen

receptors. See abstract and Table 1 on page 2776. Napolitano et al. also teaches that the compounds having 11β-substituted show high affinity for estrogen receptor (see particularly at "Introduction" page 2774).

Napolitano et al. does not expressly disclose the particular 11β-substituted estradiol herein having a length of from 5-9 carbon atoms, and the employment of these estradiol in a method for treating estrogen deficiency disorders and a method of treating estrogen deficiency disorders by inducing ER-α agonist activity and EP-β antagonist activity in a patient in need thereof.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular 11β-substituted estradiol herein in a method for treating estrogen deficiency disorders and a method of treating estrogen deficiency disorders by inducing ER-α agonist activity and EP-β antagonist activity in a patient in need thereof.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the particular 11β-substituted herein in a pharmaceutical composition and method for treating estrogen deficiency disorders since the estradiols of Napolitano are known estrogenic compounds and estradiol compounds are well known to be useful the method for treating estrogen deficiency disorders.

Moreover, the substituent at the 11 β-position in the compounds of Napolitano is known to have high binding affinity for the estrogen receptor according to Napolitano. Estrogen receptor affinity is known to discriminate two estrogen receptors, ER-α and EP-β. Therefore, one ordinary skill in the art would also have expected the estradiol

compounds of Napolitano to be useful a method of inducing ER-α agonist activity and EP-β antagonist activity in a patient.

The structure of the instant compounds having a length of from 5-9 carbon atoms in $R_{11}$, is substantially similar to the structures of their homologs having about 5 carbons or less as $R_{11}$ in Napolitano. Therefore, one of ordinary skill in the art would have reasonably expected that the instant compounds would have possess the similar activity as their homologs because of the substantially close structural relationship. It has been settled that the addition of $CH_3$ or several $CH_2$ groups to a known compound is not ordinarily patentable and prima facie obvious. See *In re Wood*, 199 USPQ 137. Thus, one of ordinary skill in the art would have reasonably expected that the instant compounds would be useful in the method for treating estrogen deficiency disorders and a method of inducing ER-α agonist activity and EP-β antagonist activity in a patient. Further, Napolitano is seen to provide the motivation to the structure modification herein since he teaches that the compounds having 11β-substituted show high affinity for estrogen receptor.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

***Response to Argument***

Applicant's arguments filed August 23, 2005 with respect to the rejections made under 35 U.S.C. 103(a) of record in the previous Office Action May 16, 2005 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art. These remarks are believed to be adequately addressed by the obvious rejections presented above.

Additionally, Applicant's results shown in Table A and B of the specification at pages 14 and 14a herein have been fully considered with respect to the nonobviousness and/or unexpected results of the claimed invention over the prior art and found persuasive as claims 2, 4, 14, and 16 since those compounds recited in these claims, for example claim 2, have shown the unexpected properties, as an **agonist** on ER-α but as an **antagonist** on EP-β, in contrast to the compounds such as Compound 2 and Compound 10 having 4 carbon behaving as an agonist on ER-α and as an agonist on EP-β.

Moreover, these results are not deemed persuasive as to claims 1, 3, 7-8, 13, and 15 since there are no unexpected results for compounds having 7-9 carbons. Thus, the evidence in the examples is also not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the claimed compounds having 7-9 carbons in the claimed pharmaceutical composition and method for treating estrogen deficiency disorders and a method of inducing ER-α agonist activity and EP-β antagonist activity in a patient in need thereof. See MPEP § 716.02(d). Therefore, the evidence presented in specification herein is not seen to be clear and convincing in support the nonobviousness of claims 1, 3, 7-8, 13, and 15 over the prior art.

Therefore, Claims 2, 4, 14, and 16 are seen allowable in view of the unexpected properties as discussed above.

***Claim Objection***

Claims 2, 4, 14, and 16 are objected to as being dependent upon a rejected base claims 1 and 13, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
Primary Examiner
Art Unit 1617
November 8, 2005